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The Lederle Bulletin

A concise presentation of authoritative information concerning the practical application and clinical value of biological therapy.

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Universal Diphtheria Immunization Now Practical

PARK conclusively demonstrated the value of diphtheria immunization with the original formula Toxin-Antitoxin, containing three L plus doses of toxin. Immunity in over 90 per cent of the children, lasted six years and possibly will continue throughout life. The original formula however, was found impractical for universal application because of the severe reactions produced in adults.

Park and his co-workers at the Research Laboratory of the New York City Department of Health have modified the formula to contain only one-tenth L plus dose of toxin.

Their studies show that this new formula confers an immunity equal to that established by the former product, and that no severe reactions occur even in older children or adults. Hence, this improved product will permit of universal immunization against diphtheria.

Toxin-Antitoxin Lederle

is made according to Park's new formula and contains one-tenth L plus dose of toxin. It is supplied in the following packages:

One vaccination in 3 vials
Ten vaccinations in 30 vials

LEDERLE ANTITOXIN LABORATORIES
511 Fifth Avenue, New York City

The Lederle Bulletin

VOL. I APRIL 1924 No. 2

The Effect of Freezing on Toxin-Antitoxin Mixtures

FOLLOWING the severe reactions that were reported in New England from the use of toxin-antitoxin that had been frozen and thawed, extensive studies have been made of the effects produced on different mixtures of toxin-antitoxin by this freezing and thawing process. The freezing in these tests was conducted at various temperatures below zero Fahrenheit for different periods of time, in an attempt to reproduce the natural conditions that might be met with in Northern winter weather.

All mixtures based on the one-tenth L plus dose passed through this series of experiments without showing any increase whatever in toxicity. A mixture containing one L plus dose per cubic centimeter showed an increase in toxicity under certain conditions of freezing and thawing so that 1 cc after freezing contained as much toxin as did 5 cc of the same mixture which had not been frozen. This degree of toxicity, the highest increase noted in any of the tests, while sufficient to give most undesirably severe reactions, could not cause permanent injury.

These studies show that the one-tenth L plus dose toxin-antitoxin mixture, which has already quite generally superseded all other mixtures, is safe and efficient for use under all conditions. These studies further support the recommendation of McCoy, Rosenau and Park, which was prepared at the request of the American Medical Association, in which they stated:

> "We recommend, in view of this occurrence, that mixtures containing the minimum practical amount of toxin (one-tenth L plus dose in an injection) be used. This mixture, we believe, will be both entirely safe and efficient."

Pollen Therapy of Hay-Fever

MEDICAL writers of the sixteenth, seventeenth and eighteenth centuries mentioned the existence of a certain form of catarrh of the mucous membranes which was correlated to the flowering period of plants, but the recognition and establishment of hay-fever as a true clinical entity must be credited to BOSTOCK, who in 1819 described it as a disease with definite symptomatology and seasonal occurrence.

GATHERING POLLINATING GRASSES

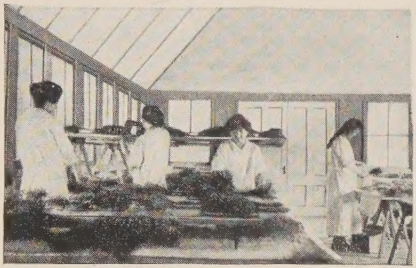
The first definite connection between the pollen of plants and hay-fever was recognized by ELLIOTSON in 1830; but the medical world is indebted to DUNBAR for the exhaustive scientific proof in 1903 of the specific action of pollen as the cause of hay-fever. DUNBAR assumed that the active substances of the pollens were true toxins, but later investigations established the fact that the active substances are proteins with active antigenic properties.

EARLY INVESTIGATIONS WITH POLLEN EXTRACTS

In 1911, NOON and FREEMAN published from WRIGHT'S laboratory in London the first scientifically conducted and controlled experiments in desensitizing hay-fever subjects by hypodermic injections of pollen extracts. NOON was the first to establish the pollen unit which he defined as the equivalent of one-millionth gram of pollen. Both he and FREEMAN succeeded in alleviating the condition of many sufferers from European or spring hay-fever by administering gradually increasing doses of extract of timothy pollen. CLOWES was the first to report a definite method of vaccination against hay-fever in this country; but to KOESSLER must be given the credit for placing the method of desensitization against hay-fever on a scientific basis, for he was the first to report a method of administering pollen ex-

tracts according to a definite scheme of dosage which proved to be safe and effective.

These investigations established beyond doubt that desensitization with extracts of pollen was possible; and further, that by this means the onset of hay-fever could often be entirely prevented when the extract was administered prior to the usual date of the attack, and that the symptoms of hay-fever could be materially alleviated when the extract was used after the disease manifested itself. However, KOESSLER emphasized the fact that *the aqueous pollen extract was not stable and that it rapidly deteriorated in potency after three or four weeks.* He pointed out that the material to be injected must be constantly of uniform potency and that no extract of pollen which he had studied could comply with this demand if it were more than three weeks old.



FLOWERING TOPS SHEDDING POLLEN

The cut ends of tops are immersed in pans of water with flowering tops overhanging glazed paper. This work is carried on in sunlit rooms protected from air currents. Under favorable conditions, the flowering tops continue to ripen and discharge their mature pollen grains for some time. Pollen grains are collected by a vacuum apparatus, sifted to remove pollen pods and other plant debris, and promptly and thoroughly dried in vacuum desiccators. The dried pollen grains are extracted in glycerol and salt solution, and the solution of pollen antigen in this medium has been proven to remain stable for several years.

THE DEVELOPMENT OF POLLEN ANTIGENS (LEDERLE)

At this stage of the investigations, research studies were begun in the LEDERLE ANTITOXIN LABORATORIES on the problem of preparing the active antigenic principle of the pollen in stable form, suitable for general distribution.

In 1914, after various methods of extracting the pollen had been used and their value carefully compared, the method of extracting the dried pollen in 66⅔ per cent glycerol and 33⅓ per cent saturated sodium chloride solution was perfected in the LEDERLE ANTITOXIN LABORATORIES. Such a glycerolated pollen antigen proved to be remarkably stable and the most potent of many extracts tested, including those made by all methods of extraction that had

been described. No loss in antigenic properties could be detected in such glycerolated pollen antigens after being stored in the icebox for 22 months.

Another important result of the research work in the LEDERLE ANTITOXIN LABORATORIES was in the standardization of the product. It was found that the glycerolated pollen antigen could be accurately standardized against anti-pollen serum by means of *the complement fixation method, whereby the amount of antigenically active protein in the extract is accurately determined and measured;* thus making it possible to establish a uniform and accurate dosage which insures the maximum degree of protection with the minimum of reaction.

STANDARDIZATION OF POLLEN ANTIGEN BY COMPLEMENT FIXATION METHOD

The first step in preparing a scientific product for clinical use is the development of some test which will accurately determine the therapeutic activity of the product. The complement fixation test was first successfully applied for standardizing pollen antigen in the LEDERLE ANTITOXIN LABORATORIES. This test proved to be a reliable method of measuring the therapeutic activity of pollen antigen. The adoption of this test as a means of standardization made it possible for the LEDERLE ANTITOXIN LABORATORIES to introduce glycerolated pollen antigen, in stable and standardized form, to the medical profession in 1914.

This was a long step forward, for previous attempts at standardization had been carried out by chemical analysis which determined the nitrogen content as an index of the amount of pollen protein present. However, as pointed out by CLOCK, *such chemical analysis does not differentiate between the antigenically active pollen protein and that which is denatured or inert.* Pollen proteins, when extracted in physiological salt solution or in dilute alcohol, become denatured and lose most of their specific antigenic properties in three to four weeks. Such extracts are, therefore, uncertain in their action as desensitizing agents unless used when freshly prepared; but they still show, even when a year or more old, the same amount of nitrogen that was present when the extract was freshly prepared. Therefore, chemical analysis by nitrogen determination is not a reliable

method of determining the antigenic power of pollen extracts.

On the other hand, only the unaltered protein which is antigenically active enters into the complement fixation reaction; autolytic cleavage products or protein split products play no part. In the glycerolated pollen antigen, the protein is preserved by the glycerol from autolytic deterioration so that the original standardization is permanent. Hence, this method of standardization and preservation of pollen protein insures accurate amounts of antigenically active pollen protein in every dose of the glycerolated pollen antigen. This stable and accurately standardized pollen antigen which was introduced to the medical profession in 1914 by the LEDERLE ANTITOXIN LABORATORIES enables the physician to obtain results of maximum value in the treatment of hay-fever patients and to avoid the undesirable results induced by extracts that have undergone deterioration.

CLINICAL RESULTS WITH POLLEN ANTIGENS

In 1922, CLOCK reported an analysis of 1578 clinical reports from physicians in all sections of the United States who had used the glycerolated pollen antigen during five consecutive years. This analysis showed an average protection or relief from hay-fever symptoms in 84 per cent of cases with a remarkable uniformity of favorable results each year in every locality. Therefore, it would seem that the method of giving prophylactic injections of the glycerolated pollen antigen early in the season offers the best means of any method thus far advanced for the preventive treatment of hay-fever.

It is no longer necessary to forsake one's business during the summer months and retire outside the zone of the offending pollinating plants. This was formerly the only rational therapeutic measure but it was also expensive and time-consuming. With the glycerolated pollen antigen treatment, however, the majority of hay-fever sufferers can be successfully desensitized and can continue to transact their business in their accustomed surroundings. Hence, the value of the glycerolated pollen antigen treatment would seem to be definitely established.

RAGWEED (*Ambrosia elatior*)

Blooms from August to October. This plant grows profusely east of the Rocky Mountains and is the most common cause of fall hay-fever. Pollen from this plant will travel ten miles in sufficient quantity to induce hay-fever.

JUNE GRASS (Blue grass, *Poa pratensis*)

This grass blooms from May to September and is an important factor in spring and summer hay-fever in all sections of the country.

TIMOTHY (*Phleum pratense*)

Grows throughout the United States and is an important cause of hay-fever from June to August.

BERMUDA GRASS (*Capriola dactylon*)

From May to September, this grass is one of the most important causes of hay-fever in the Southern and Pacific States.

Clinical Results Obtained with Bacillus Acidophilus

AT the New York State Psychiatric Institute, KOPELOFF has studied the effect of Bacillus Acidophilus Milk treatment in cases of constipation and diarrhea. He points out that it is not only important to study the influence of Bacillus acidophilus on the intestinal condition as compared with the period immediately preceding treatment, but also to note how long any changes which have been induced persist. For this reason, he observed his patients for a period of one to sixteen weeks before treatment; one to twenty-seven weeks during treatment; and from one to forty-eight weeks after treatment.

Since the transformation of the intestinal flora from the proteolytic to the aciduric type appears to depend on a mass inoculation, the importance of ingesting large numbers of viable Bacillus acidophilus cannot be overemphasized. It is common experience that frequently in treating severe cases of chronic constipation it is necessary to increase the dose before obtaining beneficial results. KOPELOFF gave as much as 1500 cc of Bacillus Acidophilus Milk and 400 grams of lactose daily in some cases before the constipated condition was alleviated.

Another practice that KOPELOFF found to be valuable in difficult cases was the use of high enemas of Bacillus Acidophilus Milk thinned with a small amount of warm water. Generally these enemas were advised to be taken on two or three successive days. While the number of patients treated was limited, yet KOPELOFF made an effort to study them in such a way as to make comparisons valid. In any event, the obvious benefits obtained by the use of Bacillus Acidophilus Milk in cases of constipation and diarrhea can scarcely be questioned.

KOPELOFF summarizes his present study as follows:

> "1. A series of thirty constipated subjects were under observation before, during and after treatment with B. acidophilus. A comparison of these periods shows that during treatment the number of normal defecations was significantly increased.
>
> "2. The beneficial influence of B. acidophilus usually persists for a considerable period of time

after treatment has been stopped. Patients have been observed for from one week to about one year after treatment, and almost without exception all have had more normal defecations after than before treatment.

"3. The use of lactose during and after ingestion of B. acidophilus does much to enhance the beneficial effects (in cases of constipation).

"4. A transformation of the intestinal flora from a proteolytic to an aciduric type as shown by microscopic and plate counts may generally be induced. Such transformation is usually accompanied by almost daily defecations regardless of the severity of the constipation.

"5. Two cases of diarrhea have been successfully treated by the ingestion of B. acidophilus."

The Cause of Scarlet Fever

OWING to the fact that Streptococcus hemolyticus has been constantly found associated with scarlet fever and its septic complications, this organism has long been considered as a possible cause of the disease. However, attempts to prove its casual relation have encountered many obstacles, chief of which has been the failure to produce experimental scarlet fever.

In 1919, DOCHEZ, AVERY and LANSFIELD developed a technic for the differentiation of biological types of Streptococcus hemolyticus. This work stimulated renewed studies on the type of streptococcus associated with scarlet fever. As a result of these studies, several investigators, including BLISS, TUNNICLIFF, CORDON, STEVENS and DOCHEZ found that the type of hemolytic streptococcus in the throats of scarlet fever patients is specific and readily distinguishable from other types of Streptococcus hemolyticus. Moreover, a careful study of the throat secretions of scarlet fever patients has demonstrated this specific type of streptococcus to be present at some time during the disease in 100 per cent of cases.

Recently, Dr. A. R. DOCHEZ has reported from the Department of Practice of Medicine in Presbyterian Hospital, Columbia University, New York City the results of his studies on this scarlatinal type of Streptococcus hemolyticus. For several years he has been endeavoring to produce in animals a disease resembling scarlet fever, by using this specific scarlatinal type of streptococcus, and his efforts have now met with success.

With special technic he has produced in guinea pigs a condition resembling certain phenomena of scarlet fever. The animals developed fever, leucocytosis and lost weight; on the second and third day they showed an erythematous flush; and on the eighth to the twelfth day more or less general desquamation appeared, most conspicuous on the pads of the feet.

Dochez then produced an immune serum and tested it experimentally for its capacity to neutralize the rash locally in the skin in human cases of scarlet fever. In all of the cases tested so far, a positive neutralization has occurred which was somewhat more conspicuous than that obtained under similar circumstances from the use of convalescent scarlatinal serum. He believes that scarlet fever may be like diphtheria in that the principal localization of the infection is in the throat where the bacteria produce a toxin which gives rise to the general symptoms and rash. The immunity is probably antitoxic in character and the blanching reaction doubtless represents the neutralization of the toxin.

The immune serum was submitted to clinical trial in a limited number of cases (thirteen) at the New Haven Hospital in New Haven, Connecticut, and the results of its therapeutic use have been reported by Blake, Trask and Lynch. In ten early cases of scarlet fever, a single intramuscular injection of 40 to 60 cc of the serum was followed by prompt and complete recovery within 12 to 24 hours. The effects were manifested by a critical fall of temperature, rapid and complete disappearance of the rash, and rapid improvement in the angina. In two extremely toxic cases, approximately 200 cc of the serum was administered in divided doses and was followed by rapid and striking improvement with complete recovery within 36 hours after the initial injection of serum. In one late case with septic complications, a single dose of 40 cc of serum was given, but it failed to produce any beneficial effect. Whether the serum will prove to be of value in late cases of scarlet fever with complications remains to be determined.

Dochez is continuing his investigations and the results of his further experimental work will be awaited with much interest. While these investigations are still incomplete, yet it is to be hoped that they will eventually lead to the development of products which can be adapted to general distribution for the needs of the practicing physician.

Acidified Whole Milk as a Routine Infant Food

Marriott and Davidson, who are connected with the department of pediatrics of Washington Medical School and the St. Louis Children's Hospital, have pointed out that cow's milk can be rendered more digestible by the addition of acid and can then be given in considerably larger amounts. They have shown that sweet cow's milk neutralizes the acid of the gastric juice to a far greater extent than does breast milk, and in this way seriously impairs normal digestive function.

On the other hand, acid milk does not neutralize the gastric juice and in this respect behaves more like breast milk. Moreover, acid milk is free from pathogenic bacteria, due to the inhibiting effect of the acid on bacterial growth. Then, too, the fineness of the curd is an added advantage. Other explanations of the favorable effect of acid milk are: stimulation of the flow of bile, pancreatic and intestinal secretions; favorable effect on absorption of fat, protein and mineral matter and stimulation of the masculature of the gastro-intestinal tract. It has also been asserted that the live lactic acid organisms present in bacterially soured milk exert a favorable action on gastro-intestinal processes. Moreover, the somewhat lowered sugar content of bacterially soured milk is believed to be a factor in rendering it more digestible by infants.

Marriott has pointed out the value of whole lactic acid milk as a food for athreptic infants. As the advantages of this type of food became evident, its use was gradually extended to other infants until, at present, approximately 90 per cent of the infants in the St. Louis Children's Hospital and 50 per cent of the infants attending the feeding clinics of the Washington University Dispensary have been fed on lactic acid milk formulas. The method has also been extensively used in a number of municipal feeding clinics of St. Louis and in the private practice of a large group of pediatricians. In all, more than 1,000 infants in St. Louis have been fed on these formulas; and the results have been so generally satisfactory that Marriott and Davidson feel that a still more general use of this type of food would be advantageous in the feeding of normal as well as of sick infants.

Pruritus of the Perineum

NOWHERE in the practice of medicine may one find an ailment so little understood and so empirically treated as pruritus of the perineum. This subject has usually been considered an incidental topic in the field of rectal and skin diseases. It has been variously termed "neurosis of the skin," a "sensory reflex," and "idiopathy."

Extensive research work on the subject of pruritus ani, vulvae and scroti has been carried out by Dr. J. F. MONTAGUE of the Bellevue Hospital Rectal Clinic, New York. He has recently prepared a monograph on this affection entitled, "Pruritus of the Perineum." After an exhaustive and scientific study of this condition, MONTAGUE has arrived at a very complete understanding of the causative factors essential to success in the treatment.

A fundamental classification of this condition comprises (1) indirect pruritus and (2) direct pruritus. After a careful consideration of the mechanism whereby pruritus is produced, MONTAGUE sets forth his own belief which briefly is as follows:

Many forms of localized pruritus formerly called "reflex," "neurotic" or "constitutional" are now explainable in a more logical manner in the light of our modern conception of physiology. Thus, whenever a viscus is the seat of a chronic inflammation, congestion, hyperplasia, hypertrophy, distention, or dilation, a stream of afferent stimuli is generated by the mechanical tension on the nerves terminating in the visceral capsule. Such stimuli are transmitted by the afferent visceral nerves to the central nervous system. These abnormal afferent impulses from the viscera lead to a stimulation of the somatic afferent nerves by creating an irritable focus in the posterior spinal ganglion; and that the function of sensation being more highly developed in the somatic afferent nerves the irritant stimulus is referred not to its true source but to the place from which such stimuli are habitually received—hence, to the skin of the pruritic zone.

This transference of sensation is exactly analogous in principle to referred pain. Clinical observation of the frequent association of visceral disease with pruritus of the perineum can be linked in a logical manner with this misreference of locali-

zation. This phenomenon is evidenced as indirect pruritus; and the fact that it is an indirect pruritus can be demonstrated by the continued existence of the pruritus after the tissue of the pruritic zone has been thoroughly anesthetized or after the superficial nerves have been severed.

Under the heading of direct pruritus are included all those various causes which affect their stimulation by direct action upon the peripheral nerve endings in the pruritic zone. The source of irritation actually causes a primary pathological condition and the direct nature of the condition can be demonstrated by the abolition of the pruritus by local anesthesia or by severance of the superficial nerves. Various local trauma, such as the fissure caused by the passage of a hard, constipated stool, or the masceration of the skin by the acrid secretions of fistulae frequently lays the foundation for bacterial infection.

Even in those cases which are not primarily infective in origin (indirect pruritus), infection may nevertheless be superinduced upon the primary cause by the scratching which is invariably brought about by the itching. Abrasions, excoriations and erosions of the skin result from the scratching and bacterial invasion then occurs. Hence, according to MONTAGUE, bacterial infection may be present or imminent in both direct and indirect pruritus.

Of great interest and therapeutic value, however, is the fact that MONTAGUE has demonstrated the presence of bacteria in the cutaneous tissues in many cases of localized pruritus. He has shown that two types of bacteria are associated with this affection; namely Staphylococcus albus, which occurs in both the superficial and deeper tissues, and B. coli, which is found in the superficial tissues. The theory once in vogue of the Streptococcus fecalis being the causative factor of this affection is shown by MONTAGUE to be erroneous for he has proven in a decisive manner that this organism is nonpathogenic and has no infective power.

MONTAGUE is of the opinion that vaccines prepared from cultures of Staphylococcus albus and B. coli, isolated from this pathological source, are applicable to the treatment of a large majority of pruritic cases. While such vaccines are not applicable to every case of pruritus of the perineum, yet there is a very large percentage of cases in which they

may be advantageously employed. According to MONTAGUE:

> "In my experience with the treatment of pruritus of the perineum I have met with most excellent results in selected cases by the combined use of B. coli and Staphylococcus vaccine . . . If then we select our cases properly, i. e., those in which by the presence of excoriations or erosions we can safely assume the presence or imminence of infection, we may be certain of gratifying results."

MONTAGUE has come to the conclusion that as an important adjunct in the treatment of cases of pruritus ani, vulvae and scroti, the use of these two vaccines must be considered. This view is supported by clinical experience at his pruritus clinic in the Rectal Department of the Bellevue Hospital Dispensary, New York, where he has made a special study of pruritus of the perineum for the past eight years.

The Dick Test

For Determining Susceptibility to Scarlet Fever

DICK and DICK have recently published from the John McCormick Institute for Infectious Diseases, Chicago, the results of a series of skin tests on 153 persons to determine susceptibility to scarlet fever. A soluble toxic substance obtained in the filtrate from cultures of the scarlatinal type of Streptococcus hemolyticus was injected intracutaneously. Positive reactions were indicated by a bright redness of the skin from two to three centimeters in diameter, with some swelling and occasionally slight tenderness.

The reaction occurs in persons who have not had scarlet fever, also in scarlet fever patients during the early stages of the disease. As the disease progresses, the reaction becomes less pronounced and is absent after recovery. This would seem to suggest the production of a neutralizing antitoxic substance as recovery from the disease takes place. This reaction is neutralized by mixing convalescent scarlatinal serum with the filtrate of the culture of Streptococcus hemolyticus.

This reaction appears to be an indication of susceptibility to scarlet fever and the absence of such a reaction would indicate immunity. In other words, it looks as if the DICK test may assume an importance in scarlet fever similar to that of the SHICK test in diphtheria.

The Common Cold

A VERY comprehensive study of colds has been made by Drs. JORDAN, NORTON and SHARP in the Department of Hygiene and Bacteriology of the University of Chicago. Data concerning some 2388 students at the University of Chicago, California Institute of Technology and the University of Texas Medical School was included in this study.

Some very interesting points are brought out in the report recently published. Thus, the authors state that a cold should not be arbitrarily assumed to be an infection of the respiratory membrane, for the clinical resemblance between some colds and any known infective process is not a close one. The statistical and laboratory data indicates that the common cold is not a simple type of infection, perhaps in some instances not even an infectious process at all.

Numerous factors are undoubtedly concerned in the production of a cold. The evidence presented by these authors does not support the view that a cold is always due primarily to the entrance of some virus from without the body. On the contrary, it appears that internal body changes may be the more important factors and these in turn are closely associated with outside influences.

It is popularly supposed that those persons who keep themselves in excellent physical condition, who exercise regularly and who sleep with windows wide open, are less liable to respiratory disorders than those not following such practices. The statistics of these authors indicate that this may not always be true, and that exposure to cold air as a preventive of colds may not always be as successful as supposed. The authors conclude:

> "The common cold generally starts in the nose. About one-third of these colds extend to the chest. Resistance building practices apparently had little effect on the frequency of colds. Our data do not show that nose or throat operations result in a marked reduction of the frequency of colds. Among the bacteria cultivable on blood-agar plates, no one bacterium or group of bacteria has been found to predominate in the upper respiratory tract during a cold. Whether or not a cold is a result of a specific infectious process is unknown. It is clear, however, that outside influences, particularly those involving chilling of the body, may serve to induce a cold even if these influences cannot be regarded as the most important etiologic factor."

Bacillus Acidophilus Milk Used in Tuberculosis Sanatorium

ONE of the principal difficulties that arise in the practice of every sanatorium physician, according to Dr. WILLIAM H. MORRISS, is the proper care of the manifold gastrointestinal complications that occur so frequently in any group of tuberculosis patients. The work of Professor RETTGER with Bacillus Acidophilus attracted the attention of MORRISS who, after consultation with RETTGER, determined to employ treatment with Bacillus Acidophilus Milk at Gaylord Farm in Wallingford, Connecticut. The experiments were carefully controlled by bacteriological examinations of the stools at weekly intervals.

Three groups of patients were selected for treatment: (1) six cases having diarrhea of a more or less chronic type; (2) thirteen cases with chronic digestive disorders, characterized by gastric and intestinal gas, nausea and vomiting, sensation of fullness and discomfort and loss of appetite; (3) four cases of obstinate constipation.

The daily amount of Bacillus Acidophilus Milk given to each patient was one quart. The duration of the treatment varied from ten days to one year; the average length of treatment being three and one-half months.

Clinical results were as follows: (1) In the diarrhea group, relief of diarrhea occurred in every case; (2) in the indigestion group, improvement followed in nine out of thirteen cases; (3) in the constipation group, three out of the four cases showed improvement. The number of cases of constipation treated is too small to warrant any generalizations, but Morriss says it seems probable that satisfactory results can be obtained even in the most obstinate cases if the patient is willing to cooperate and if enough care is given to the regulation of dosage.

MORRISS believes that his study of these 23 patients suffering with various gastrointestinal disorders has shown Bacillus Acidophilus Milk to be of value. It seems quite probable, according to MORRISS, that while constipation is relieved by some bacterial reaction, the diarrhea and digestive disturbances are more benefited by some biochemical reaction.

Convalescent Serum in the Prophylaxis of Measles

SOME very interesting work on measles prophylaxis was carried out by WEAVER and CROOKS during the spring and summer of 1923. Measles is so universal that many people consider it a trivial disease; but as a cause of death in children, it ranks third from the highest among the acute contagious diseases. The report of the United States Census Bureau for 1920 shows that in the registration area of the United States there were 7,712 deaths from measles; and of these, 78 per cent were of children under five years of age. In England, out of 14,000 persons, more than 97 per cent of those over fifteen years of age had had measles.

Many American hospitals having a large children's department are confronted with outbreaks of measles almost every spring. Therefore, some method of protection against measles is needed, especially for children under five years of age; because, if the disease could be prevented until later in childhood, the mortality would be considerably reduced. The use of serum obtained from patients convalescent from measles gives promise of such protection.

The first report of a child successfully protected by this means was published in 1918. Since that time, several other investigators in Europe, South America and the United States have reported the successful use of convalescent serum as a means of immunizing children against measles. A recent summary of all the reported cases shows that convalescent serum has been used in about 2,000 cases and that it has failed to protect in less than 3 per cent, probably due to faulty technic.

At the Durand Hospital in Chicago, 57 susceptible children were under observation. Nine of these children were not given serum, and they all developed measles in from twelve to fifteen days after exposure. The serum was administered to forty-eight children; and of these, forty-four did not develop measles, although they were kept with the others and were similarly exposed.

Four of those to whom serum was given developed measles in from one to fifteen days after the administration of the serum. The authors believe that in three of these four cases, the serum was given too late.

Weaver and Crooks point out that children who have had measles, and babies during the first few months of life, do not readily contract measles. Also, that the serum must apparently be given during the first week after exposure in order to be effective.

The serum was injected deep into the muscles of the thigh in doses of 5 to 10 cc, depending upon the age of the patient and the time that had elapsed since exposure to the disease. In regard to immunity, the authors state that two months is probably the limit of the immunity produced by the serum injections.

During the year 1923, this method of preventing measles was used as a routine measure in the contagious disease hospitals of the New York City Department of Health. The results were so favorable that the Department of Health has now made the serum available to all physicians in New York City. The work of supplying the serum for the entire city is being developed under the direction of Dr. William H. Park. As the supply of serum is somewhat limited, it will be furnished to physicians for exclusive use among children under three years of age, if less than seven days have elapsed since they were exposed to measles. The serum will also be supplied to all institutions where measles might spread from older children and imperil others, and for use among children who are invalids. The serum is supplied in vials holding about 4 cc which is the immunizing dose recommended for a child under two years of age. For older children, the dose is 8 cc. It has been proven that the serum is almost always effective as a preventive if given within four days after exposure. Even if five or six days have elapsed, the serum may prevent the development of infection or at least greatly moderate its severity.

While the convalescent serum apparently remains potent for several months, its usefulness would be considerably enhanced if a supply from other than a human source were available. Nevertheless, the comparatively limited use thus far of the convalescent serum marks an important forward step in the development of preventive medicine.

Therapeutic Value of Antipneumococcic Serum

IN a clinical study of 198 cases of lobar pneumonia at the Johns-Hopkins Hospital, a very interesting point is brought out by Dr. ARTHUR L. BLOOMFIELD. He says that many physicians believe antipneumococcic serum must be given during the first three days of the disease if the serum treatment is to be effective. His tables, however, showing the result of blood cultures, indicate that as long as the blood is sterile, the greatest benefit is derived from serum therapy regardless of the day of the disease. On the other hand, less benefit follows from serum therapy in cases with bacteremia, even if treated on the second and third day

BLOOMFIELD believes that this clinical study of pneumonia cases covering a period of ten years from 1913 to 1923, reinforces the view that Type I antipneumococcic serum is of real value. He states that the serum appears indicated in all cases, regardless of the day of disease, save those in which an overwhelming bacteremia is present.

Action of Bacillus Acidophilus

AT the department of hygiene of Cornell University Medical College, research studies were conducted by TORREY and KAHN in an effort to determine the mode of action whereby B. Acidophilus is able to inhibit the growth and activity of the proteolytic organisms native to the intestinal tract, namely the putrefactive anaerobes. They had previously observed that the overgrowth of B. Acidophilus in the intestines of both dogs and humans causes a practically complete elimination of these bacteria from the intestinal tract.

Their experiments demonstrated that when B. Acidophilus is grown in association with each of several varieties of proteolytic spore-bearing anaerobes, including B. sporogenes, B. histolyticus, and B. botulinus in a medium favorable to both, proteolysis of solidified egg albumen cubes is prevented for a period of ten days

or more in the presence of 0.5 per cent glucose. The control tubes showed advanced digestion in three or four days. Furthermore, if these bacteria are grown in association in milk, digestion of the casein is inhibited indefinitely, whereas in the control cultures it is marked in two or three days.

They conclude that the inhibition of the putrefactive bacteria by B. Acidophilus seems to be dependent entirely on the lactic acid produced by B. Acidophilus; for they were not able to detect, in the fluid cultures of B. Acidophilus, any inhibitory product for the putrefactive anaerobes other than acidity.

Typhoid Vaccination

AN experimental study by NICHOLS and STIMMEL at the laboratory of the Army Medical School in Washington has brought out several interesting points concerning protection against typhoid infections by vaccination.

First. Saline vaccine proved to be more effective than lipo-vaccine, sensitized vaccine or supernatant fluid vaccine.

Second. A relatively fresh vaccine gave better protection than an old one; the period of maximum efficiency being about the first eight months.

Third. Acquired immunity is a variable factor and depends somewhat on the dose of vaccine. A high degree of immunity can be produced by sufficient vaccination, but the immunity can be overcome if the infecting dose is large enough.

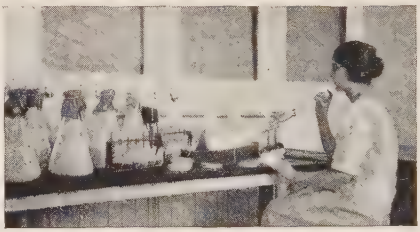
Fourth. Repeated doses give better immunity than a single dose. This probably explains the freedom from typhoid fever in the Army where the men are vaccinated every three years for three consecutive periods.

Fifth. Of the three kinds of vaccine studied, the best protection is afforded by multiple doses of a saline vaccine.

Sixth. Plain typhoid vaccine gives no adequate protection against infections with the paratyphoid A and B bacilli. This fact was demonstrated on the Mexican Border before the War and again in the British Army. Typhoid-paratyphoid vaccine has, however, proved effective.

How the Manufacture of Bacillus Acidophilus Milk Differs from "Beverage Sour Milks"

IN the manufacture of Bacillus Acidophilus Milk (Lederle), bacteriological control is required to a degree that is unnecessary in the preparation of ordinary "sour milk beverages." This is explained by the fact that the Bacillus Acidolphus is slow growing as compared with organisms which usually contaminate milk; and if milk containing other organisms (native or pasteurized milk) is inoculated with even comparatively large volumes of the most active cultures of Bacillus Acidophilus, the more rapid growth of the contaminating organisms will overgrow the Bacillus Acidophilus so that the resultant product will be unfit for use. For this reason, a safe preparation of Bacillus Acidophilus Milk can be made only where there are complete facilities for bacteriological control of the product in every step of its manufacture.



PREPARATION OF SEED CULTURES OF BACILLUS ACIDOPHILUS IN MILK

Milk positively sterilized by steam pressure is used for the development of sufficient culture of Bacillus Acidophilus for the mass inoculation of the large batches of Bacillus Acidophilus Milk (Lederle) which are sterilized and incubated in jacketed glass-lined steel tanks, specially constructed for the purpose. Every transfer of Bacillus Acidophilus culture from one seed flask to another and from the seed flasks to the tanks is adequately controlled by fermentation tube and agar plate inoculations and by microscopic examination. The operator in this picture is transferring the milk culture of Bacillus Acidophilus from a seed flask of sterile milk which is thereby inoculated from the culture.

In the routine preparation of each batch of Bacillus Acidophilus Milk (Lederle) there are four separate and complete bacteriological studies.

First, the original stock cultures are examined for purity of growth by agar plates and by fermentation tests in special sugar media.

Second, the growth in a single flask from the stock culture is like-

wise examined.

Third, twenty or more flasks are inoculated from this single flask. These contain milk to approximately 5 per cent of the volume of the batch of milk in the tanks to be inoculated for the finished product. The growth in these flasks is examined as above.

Fourth, the finished, bottled Bacillus Acidophilus Milk (Lederle) is examined in a similar manner.

Bacillus Acidophilus Milk in Chronic Intestinal Conditions

THE effect of feeding Bacillus Acidophilus Milk in chronic intestinal conditions has recently been studied by Dr. GEORGE C. MIZELL of Atlanta, Georgia. The object of his investigation was to determine the influence of Bacillus Acidophilus Milk therapy upon the symptoms and the urinary products of intestinal putrefaction. His clinical experience had shown that the urinary findings could be depended upon as an index to the putrefactive toxemia and that the symptoms of toxemia parallel the urinary findings.

FINAL BACTERIOLOGICAL STUDY OF BACILLUS ACIDOPHILUS MILK (LEDERLE)

Every lot of Bacillus Acidophilus Milk (Lederle) is examined by the microscopic study of smears and developed agar plates to determine the purity of the culture and the approximate count of living Bacillus Acidophilus in each cubic centimeter of the milk. This picture shows the inoculation of agar plates with dilutions of 1:100, 1:10,000 and 1:1,000,000 of Bacillus Acidophilus Milk (Lederle) from bottles taken from the stock ready for distribution.

For the purpose of this study, MIZELL chose two groups of patients. One group consisted of those in whom chronic intestinal toxemia of the putrefactive type had been demonstrated by laboratory findings. In the other group were patients suffering from chronic intestinal stasis and colitis.

The chief symptoms of the toxemia group were headache, aching limbs, despondency and gas. Those

of the stasis and colitis group included marked abdominal pain and soreness, together with gas.

Both groups of patients were chronic intestinal invalids and had been in such a condition, more or less, for years. Their state of health was, perhaps, worse than is suggested by the above list of symptoms. Seventy-five per cent of them had had various surgical operations, varying from thyroidectomy to hysterectomy. Thirty-five per cent had demonstrable post-operative conditions, especially of the stomach, such as achylia, chronic gastritis, or gastrectasis.

Examination of Whey Agar Plates of Bacillus Acidophilus

This examination determines the purity of the culture and the number of organisms per cubic centimeter. Colonies of Bacillus Acidophilus in agar are so minute that they are observable with difficulty, except with the aid of a powerful lens or a microscope.

Therefore, Mizell believes that the test of the remedy was a severe one, but that the observations were none the less instructive even though in most cases he was dealing with a secondary condition. The Bacillus Acidophilus Milk treatment was administered over a period varying from two to six months; the average length of the treatment being three months.

In the group of chronic intestinal toxemia, therapeutic results were obtained in 40 per cent of the cases as shown by relief of symptoms, stasis and indicanuria. In the group of intestinal stasis and colitis, therapeutic results were secured in 60 per cent of the cases as was proved by relief of symptoms and stasis. In all of those who were relieved of the toxic symptoms and stasis (Group I) and of colitis and stasis (Group II), general improvement in the way of gain in weight, in quality of blood, and strength was observed.

MIZELL feels that the results are highly satisfactory. He concludes:

"Finally, subject to the limitation of this small clinical study, the following conclusions appear permissible:

"(1) Relief from chronic intestinal toxemia, putrefactive type, and stasis even in the presence of intestinal adhesions has been secured while feeding Bacillus Acidophilus Milk cultures in conjunction with a general diet.

"(2) Chronic ileo-colon and colon stasis of undetermined origin as well as secondary to intestinal adhesions may be relieved by feeding Bacillus Acidophilus Milk."

In the discussion which followed the presentation of MIZELL's paper before the Southern Gastro-Enterological Association, Dr. C. C. BASS, professor of experimental medicine in Tulane University of Louisiana, emphasized the importance of large doses of Bacillus Acidophilus Milk because the Bacillus Acidophilus multiplies at a much slower rate than does the colon bacillus which is already present in large numbers in the intestine. He said:

"If the culture can be made to be a very pleasant food beverage, which the milk culture is, the treatment would not be difficult to carry out, provided an adequate supply of the acidophilus milk culture can be obtained."

Pruritus Vaccine Treatment

Lederle

(MONTAGUE *Method*)

THIS treatment is based on the researches of DR. J. F. MONTAGUE of the Bellevue Hospital Rectal Clinic, New York. It consists of vaccines prepared from the only two bacterial types that MONTAGUE has demonstrated to be the inciting or contributory factors in pruritus of the perineum.

Two vaccines are used in the treatment: (1) Staphylococcus albus and (2) B. coli. This vaccine treatment has been very carefully prepared to fulfill all of the recommendations of MONTAGUE, as outlined in his monograph "Pruritus of the Perineum."

Pruritus Vaccine Treatment (Lederle) is supplied in packages containing 10 graduated doses of vaccine made from Staphylococcus albus and 7 graduated doses of vaccine prepared from B. coli. These vaccines are furnished in concentrated glycerol suspension; each dose of vaccine being accompanied by a vial of diluent.

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